General

Guideline Title

Teriflunomide for treating relapsing–remitting multiple sclerosis.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jan. 57 p. (Technology appraisal guidance; no. 303).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Teriflunomide is recommended for treating adults with active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if

- They do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis and
- The manufacturer provides teriflunomide with the discount agreed in the patient access scheme.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Active relapsing–remitting multiple sclerosis

Guideline Category

Assessment of Therapeutic Effectiveness

Technology Assessment

Clinical Specialty

Family Practice

Neurology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of teriflunomide for treating relapsing–remitting multiple sclerosis

Target Population

Adult patients with relapsing–remitting multiple sclerosis

Interventions and Practices Considered

Teriflunomide

Major Outcomes Considered

- Clinical effectiveness
  - Relapse rate
  - Severity of relapse
  - Disability
  - Symptoms of multiple sclerosis
  - Freedom of disease activity
  - Mortality
  - Adverse effects of treatment
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE), University of York (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Searches

The manufacturer's submission described the search strategies used to identify relevant clinical effectiveness studies about the use of teriflunomide for the treatment of relapsing–remitting multiple sclerosis (RRMS) in adults.

The electronic databases MEDLINE and MEDLINE In-Process (via PubMed), EMBASE (via Embase.com) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify clinical studies on the use of teriflunomide and other comparators. In addition to this, grey literature was searched in several medical society and regulatory body Web sites and a hand search was carried out.

Searches were conducted in May 2012 and subsequently updated on 12 November 2012. The searches covered the period 1st January 1980–November 12 2012, were limited to English language publications, and excluded letters, editorials, comments and animal studies.

Overall the searches were appropriate and well documented, and included the use of both subject indexing terms (MeSH and EMTREE) and free text searching. Field searching, Boolean operators and truncation were used where required. All the databases required by NICE were searched, though only CENTRAL was searched in the Cochrane Library when it might have been useful to have searched the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. For this reason the manufacturer missed a protocol of a Cochrane Systematic Review on teriflunomide for the treatment of multiple sclerosis that is finished and published now.

The trade name of teriflunomide and the trade name of its comparators were not included in the search strategies. It is possible (though not likely) that potentially useful records were not retrieved. The search strategies used in the manufacturer's submission were limited to experimental trials. However a search for other study designs such as cohort or case control studies may have provided useful supplementary information about safety. It is not clear if the methodological search filters used in PubMed and EMBASE were derived from validated search filters.

Inclusion Criteria

The manufacturer outlined appropriate inclusion criteria for population, interventions and comparators, outcomes and study designs. It is noted that eligibility criteria for the review included patients with secondary progressive multiple sclerosis (SPMS). All included direct trials of teriflunomide had a small percentage of patients with SPMS (at least 87% were patients with RRMS). The Committee considered this to be overall acceptable but it is noted, in contrast, that the trials in the mixed treatment comparison (MTC) largely had 100% RRMS.

The manufacturer included open-label extension studies in addition to randomised controlled trials (RCTs) in order to assess long-term safety of teriflunomide. This approach is acceptable. However the efficacy data from these trials should be treated with some caution as there is no concurrent placebo group and therefore no information on natural course of disease.

The restriction to English language trials only could have led to trials being missed but in this instance the ERG is unaware of any missing trials. The manufacturer's flow diagram does not include data (no. of studies, etc.) included and excluded from the direct evidence.

Cost-effectiveness

Searches

The manufacturer's submission described the search strategies used to identify cost-effectiveness studies relevant to this appraisal of teriflunomide for the treatment of relapsing-remitting multiple sclerosis in adults.

The electronic databases MEDLINE, MEDLINE In-Process (via EMBASE) and EMBASE (via EMBASE), EconLit (Ovid), the Cochrane Library (Wiley) including the NHS Economic Evaluation Database (NHS EED) were searched. In addition to this, a grey literature search was

performed.

Database searches were performed on 10th and 11th October 2012. Search strategies for each database were documented. The searches covered the period 1966–October 2012 for MEDLINE and EMBASE, 1961–October 2012 for Econlit and 1968–October 2012 for NHS EED. No language or date limits were applied to the search. The search excluded animal studies as well as the publication types 'letter' and 'editorial', and 'note'.

The searches were appropriate and comprehensive, and included the use of both subject indexing terms and free text searching. Field searching, Boolean operators and truncation were used where required. All NICE required databases were searched, as well as medical society and regulatory body websites.

A methodological search filter adapted from the Scottish Intercollegiate Guidelines Network Grading (SIGN) was included to identify economic studies and utilities in MEDLINE and EMBASE. The adapted economic study design search filter may have excluded potentially useful records from MEDLINE and EMBASE.

The addition of the following EMTREE terms would have improved the filter used in EMBASE and MEDLINE: 'Economic evaluation' and 'Cost utility'.

An important issue is that the manufacturer didn't adapt the search for MEDLINE, instead they searched EMBASE and MEDLINE together from the EMBASE interface. They used the same search and the same methodological filter developed for EMBASE. The Cochrane Manual advises to adapt the searches to every database.

Conclusions

The systematic review of the literature resulted in no cost-effectiveness analyses of teriflunomide. Two cost-effectiveness analyses of other treatments were identified to help inform the development of the *de novo* model.

Number of Source Documents

Clinical Effectiveness

3 placebo-controlled trials, 2 extension studies, and 1 phase II trial of teriflunomide

Cost-effectiveness

2 cost-effectiveness analyses of other treatments were identified to help inform the development of the *de novo* model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and

prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics, University of York (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Data Extraction

Details of data extraction methods were not provided (such as number of reviewers involved and procedures to avoid errors and bias). The ERG could not, therefore, comment on the robustness of the data extraction methods.

Quality Assessment

The manufacturer's quality assessment was adapted from the Centre for Reviews and Dissemination (CRD) guidance covering: randomisation, allocation concealment, similarity of groups at outset, blinding, differential dropout, under-reporting of outcomes and use of intention to treat analysis. This tool was appropriate. Trials of both direct evidence and those included in the base case mixed treatment comparison (MTC) were assessed. No quality data were provided for the trials included in the sensitivity analysis of the mixed treatment comparison (trials conducted post 2000 and ≥80% relapsing–remitting multiple sclerosis [RRMS]).

Evidence Synthesis

The manufacturer undertook a meta-analysis of all the three placebo-controlled trials (Study 2001, TEMSO and TOWER) using a random-effects model. A random effects model may not have been appropriate due to the small number of studies (2 or 3 in each analysis). The manufacturer checked for statistical heterogeneity and clinical diversity and did not find major issues of heterogeneity.

The study of teriflunomide vs. Rebif 44µg (TENERE) was not included in the meta-analysis as there was no placebo arm. This was appropriate. Results of the trial were tabulated and synthesised narratively.

To supplement the direct evidence the manufacturer conducted a MTC indirectly comparing eleven licensed and unlicensed drugs including beta-interferon and glatiramer acetate.

Safety data from randomised controlled trials (RCTs) and trial extensions were presented individually. A pooled analysis was conducted using adverse event data from Study 2001 and TEMSO only.

See Section 4 of the ERG report (see the "Availability of Companion Documents" field) for more information and a critique of methods conducted by the ERG.

Cost-effectiveness

The systematic review of the literature resulted in no cost-effectiveness analyses of teriflunomide. Two cost-effectiveness analyses of other treatments were identified to help inform the development of the *de novo* model. See Sections 5 and 6 in the ERG report (see the "Availability of Companion Documents" field) for extensive discussions of the manufacturer's economic evaluation, the ERG's critique of the model, and addition ERG analyses.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-effectiveness

Availability and Nature of Evidence

The manufacturer provided a de novo economic model, which the Committee understood to be structurally similar to models used in previous National Institute for Health and Care Excellence (NICE) technology appraisals.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee acknowledged that there were still some uncertainties in the economic analyses relating to whether treatment waning would occur, the amount of non-health costs that should be considered, and the fact that the benefits of oral treatment are not captured in the quality-adjusted life years (QALYs).

The Committee noted the Evidence Review Group's (ERG's) concern about the external validity of the manufacturer's model, and discussed the external validation presented by the manufacturer in response to the appraisal consultation document. The Committee noted that the incremental cost-effectiveness ratios (ICERs) estimated by the manufacturer's revised model were substantially higher than those in NICE technology appraisal guidance 32 for most of the comparators. The Committee noted the considerable uncertainty in the current analyses, and the analyses carried out for NICE technology appraisal guidance 32 , and acknowledged that showing close convergence between the previous and present analyses was challenging. The Committee concluded that the manufacturer's model was sufficiently valid for decision-making in the current appraisal.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee concluded that the quality-of-life benefits of an oral treatment were not fully captured in the QALY.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

No

What Are the Key Drivers of Cost-effectiveness?

The Committee was aware that the key drivers of the economic model were the choice of comparator, disease progression, the natural history, the rate of transition to secondary progressive multiple sclerosis, and health-related quality of life associated with more severe health states.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee concluded that teriflunomide dominated the beta interferons. For the comparison with glatiramer acetate, the Committee noted the varying ICERs from the different analyses but accounting for the benefits not captured in the QALY, such as the oral administration of teriflunomide, the Committee concluded that, on balance, the most plausible ICER for teriflunomide compared with glatiramer acetate would be below £20,000 per QALY gained.

See Section 4 in the original guideline document for additional information.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of teriflunomide and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from randomised controlled trials, a phase II trial, and extension studies. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of teriflunomide for treating relapsing–remitting multiple sclerosis

Potential Harms

The summary of product characteristics lists the following adverse effects for teriflunomide: diarrhoea, alopecia, nausea and increased levels of alanine aminotransferase. For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has active relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that teriflunomide is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the manufacturer have agreed that teriflunomide will be available to the NHS with a patient access scheme, which makes teriflunomide available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations.
- NICE has developed tools to help organisations put this guidance into practice. These are available on the NICE Web site (see also the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jan. 57 p. (Technology appraisal guidance; no. 303).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Jan

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Teriflunomide for treating relapsing–remitting multiple sclerosis. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jan. (Technology appraisal guidance; no. 303). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Fayter D, Spackman E, Epstein D, Palmer S, Rodriguez-Lopez R, Woolacott N. Teriflunomide for treating relapsing forms of multiple sclerosis. A single technology appraisal. York (UK): CRD and CHE Technology Assessment Group; 2013. 139 p. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .

Patient Resources

The following is available:

- Teriflunomide for relapsing–remitting multiple sclerosis. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jan. (Technology appraisal guidance; no. 303). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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